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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,443	08/14/2001	Jack Price	GJE-74	9647

23557 7590 07/03/2003

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	4

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/913,443	Applicant(s) PRICE, JACK	
	Examiner Celine X Qian	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-7, 10-14 are pending in the application.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The specification is objected to because of lack of detailed disclosure regarding stem cell transplantation. The specification discloses on page 6 line 12 "as details in the abstract," however, the abstract does not contain detailed information regarding stem cell transplantation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 10-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior

art; (d) the relative skill of those in the art; (e) the level of predictability in the art; (f) the amount of direction provided by the inventor; (g) the existence of working examples; and (h) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue" (MPEP 2164.(a)).

Nature of the invention:

The nature of the invention is a method for treating a sensory, motor and /or cognitive deficit including Alzheimer's disease, Parkinson's disease, Korsakoff's disease and Creuzfeld-Jacob disease, by intracerebral administration of a hematopoietic stem cell to the patient. The claim is further drawn to such method wherein the hematopoietic stem cell is conditionally immortal, expresses an temperature sensitive oncogene or a therapeutic heterologous gene product, and a pharmaceutical composition comprising said hematopoietic stem cell.

The breadth of the claim:

The breadth of the claims is very broad. In the instant case, the broadest claim encompasses a method of treating any type of sensory, motor and/or cognitive deficit by intracerebral administration of a single hematopoietic stem cell. The claims are further drawn to such methods of treating sensory, motor and/or cognitive deficit by a genetically modified hematopoietic cell, for example, a hematopoietic cell comprising a therapeutic gene.

Amount of guidance in the specification and Working Examples:

The teaching of the specification is very limited. The specification only discloses that bone marrow cells including hematopoietic stem cells and mesenchymal stem cells exhibit neuronal and astrocyte specific markers after intracerebral transplantation to the mouse ischaemic striatum following middle cerebral artery occlusion. The specification does not

provide any details regarding what type of hematopoietic stem cells (for example, human, rat, mouse?) were transplanted into mice, and what is their post transplantation phenotype. The specification fails to teach a method of treating a sensory, motor and/or cognitive deficit such as Alzheimer's disease or Parkinson's disease by administering the hematopoietic cell in a mouse model. The specification also fails to teach whether a human hematopoietic stem cell can differentiate into a neuronal cell *in vivo*. Moreover, the specification fails to teach a method of treating a sensory, motor and/or cognitive deficit in human by intracerebral administration of a hematopoietic stem cell with or without a therapeutic gene product or a pharmaceutical composition comprising said hematopoietic stem cell. Without teaching from the specification, one skilled in the art would have to turn to prior art for guidance to practice the claimed method.

State of the Art, Predictability or Unpredictability of the art, Amount of experimentation necessary and Skill level of the artisan:

The state of art at the time of filing considers stem cell and/or gene therapy unpredictable. Although Chopp et al. (1999, Society for neuroscience, Vol 25, abstract no. 528.2) and Mezey et al. (2000, European Journal of Pharmacology, Vol 405, pp. 297-302) provide some evidence that hematopoietic stem cell has potential to develop into neurons, glial cells and astrocytes in some regions of brain upon intracerebral transplantation, both references fail to teach whether such transplantation would achieve therapeutic effect on any sensory, motor and/or cognitive deficit. Mezey et al. further point out that there are many questions remain to be answered before hematopoietic stem cell may be used as a source for treating neurodegenerative disease. Such questions include what type of growth factor is required for enrich, instruct or select distinct CNS cell types; are there any temporal limits dictating when cells across the blood brain barrier,

and if so, what is the optimal entry routes for transplanting cells; or whether bone marrow derived cells need to pass through the general circulation or be exposed to the cerebral spinal fluid of the central nervous system before acquiring their neuronal potential; which population from bone marrow stem cells (hematopoietic or stromal stem cells) differentiate into glial or neuronal cell; and most importantly, whether human hematopoietic cell has the similar "neural" potential (see page 301, 1st col., 2nd paragraph). In a recent review published by NIH (three years after applicant's priority date), it also states "evidence that specialized cells generated from human stem cells can replace damaged or diseased cells and tissue" raises "more questions than answers" at present (see page ES-5, 2nd col., bottom paragraph). The review also indicates that not all information from mouse stem cells can be translated to understanding of human stem cells because mouse and human cells differ in significant ways (see page ES-6, 1st col., 1st paragraph). When discussing the potential of using adult stem cells as a source for repairing neuronal damage such as in Parkinson's disease, the author indicates that although stem cells from hematopoietic origin can be coaxed to express cell surface markers characteristic of nervous system, it is not clear whether these cells are capable of giving rise to fully functional neurons. Moreover, the author states that "no one has yet published evidence that cells from any renewable source that are laboratory-directed to differentiate into dopamine neurons can eliminate symptoms in animal models of Parkinson's when implanted," and concludes that a great deal of basic research remains to be done to find what type of stem cells, including fetal cells, embryonic stem cells and adult stem cells, provides the best way to get a workable therapy for Parkinson's disease. Therefore, in view of the teaching from the prior art, stem cell therapy

is still at an experimental stage, and whether intracerebral implantation of a hematopoietic cell can treat a sensory, motor and/or cognitive deficit is unpredictable.

The state of art at the time of filing considers the success of gene therapy as unpredictable. The NIH review states that the potential success of gene therapy technology depends on the delivery of the therapeutic transgene into the appropriate human target cells and the ability of the gene to function properly in the cell, both of which pose considerable technical challenges (see page 99, 2nd col., 1st paragraph). Verma et al. (1997, Nature, Vol. 389, pages 239-242), Anderson et al.(1998, Nature, Vol. 392, pages 25-30), and Palu et al.(1999, Journal of Biotechnology, Vol. 68, pages 1-13) also discuss the inherent difficulties in gene therapy. The major difficulties include poor delivery systems and poor gene expression after delivery (see Anderson, page 30, 1st col., 5th paragraph). In *ex vivo* gene therapy, transcriptional silencing is an obstacle that prevents sufficient gene expression to achieve therapeutic level. In addition, efficient transplantation is another challenge to *ex vivo* gene therapy. As Verma et al. indicate that attempts to repeat long-term myoblast transplantation in hemophiliac dogs led to only short-term expression because the infected dog myoblasts could not fuse with the muscle fibers (see page 240, 3rd col., 1st paragraph). Although hematopoietic system may offer an advantage for *ex vivo* gene therapy because resting stem cells can be stimulated to divide *in vitro* using growth factor and the transplantation technology is well established, there is still a lack of good enhancer-promoter combination that allow sustained production of high levels of protein in these cells (see Verma, page 240, 3rd col., 1st paragraph). In addition, the percentage of stem cells that actually receive the therapeutic gene has usually been too low to obtain a therapeutic effect (see NIH review, page 102, 2nd col., 2nd paragraph). Another factor that affects the efficacy of gene

therapy methods is the immune system of the host organism (see Palu, page 9; 1st col., 2nd paragraph, lines 1-5 and NIH review, page 103 2nd col., 3rd paragraph). The host immune system rejects the foreign cell that is introduced to said host thus prevents the expression of the gene within the cell. Therefore, in view of the above technical difficulties, whether intracerebral implantation of a hematopoietic cell comprising a therapeutic gene can treat a sensory, motor and/or cognitive deficit is unpredictable.

In summary, the claimed method is not enabled at time of filing because the specification does not teach how to overcome the technical difficulties and unpredictability in the art of stem cell and gene therapy. Without teaching from the specification, one skilled in the art would have to engage in undue experimentation to use the pharmaceutical composition comprising a hematopoietic stem cell and practice the method as claimed. Therefore, the claims are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The word "haemapopietic" renders the claims indefinite because the meaning of this word is not known. It appears that the word is a misspell of "hematopoietic," appropriate correction is required.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 30, 2003

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER